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We studied the toxicity and antitumor activity of Liposomal-Annamycin in patients with metastatic breast carcinoma. Sixteen patients were treated. Toxicity was mild and consisted mostly of bone marrow suppression, particularly granulocytopenia. Non-hematological toxicity was less than what is usually seen with other anthracyclines. No responses were seen.

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INTRODUCTION

Liposomal-Annamycin is a liposome entrapped new anthracycline antibiotic, which has shown lack of cross-resistance in vitro and in vivo in different cell lines that express P-glycoprotein and MRP. In a Phase I study conducted in patients with solid tumors, the dose limiting toxicity was myelosuppression . No alopecia, muositis, cardiac, skin, nor gastrointestinal toxicities were observed. The maximum tolerated dose was 210 mg/m^2 administered intravenously every 3 weeks. Because the multidrug resistance phenotype has been associated with some human malignancies, particularly acute leukemia and breast carcinoma, when they become refractory to standard chemotherapy, we performed a Phase II clinical study of liposomal-Annamycin in patients with metastatic breast carcinoma refractory to doxorubicin. This report summarizes the results of this study.

REPORT

The study accrued a total of 16 patients. No clinical responses were observed. We conclude that Liposomal-Annamycin is an inactive agent in this heavily pretreated patient population.

OBJECTIVE OF THE STUDY

1. To evaluate the antitumor activity of Liposomal-Annamycin in patients with metastatic breast carcinoma resistant to anthracyclines.
2. To correlate responses with MDR-1 expression in tumor tissue.

ELIGIBIBILTY CRITERIA

1. Metastatic breast carcinoma
2. Anthracycline-resistant. Amended during the last year to allow accrual of patients who have received prior anthracyclines in the adjuvant setting, but in whom there is no demonstration of clinical resistance to anthracyclines. This modification was introduced to test Liposomal-Annamycin in a less heavily pretreated population since no responses were seen in the first 14 patients.
3. Measurable disease
4. Life expectancy >12 weeks
5. Prior anthracycline <350 mg/m^2 of doxorubicin equivalent by bolus, <450 mg/m^2 by prolonged infusion
6. Adequate bone marrow function
7. Ejection fraction >55%

PATIENT CHARACTERISTICS

A total of sixteen patients were entered in the study. The recommended dose was 190mg/m^2. It was escalated to 210 mg/m2 in 8 courses and to 250 mg/m2 in 2 courses. The following Table summarized the characteristics of the patients entered.

Number of patients entered	16
Number of patients evaluable	16
Age median (range)	47 (34-73)
Performance status	
1	14
2	2
Sex: female	16
Race:	
Black	7
Hispanic	4
White	5
Histology	
Ductal carcinoma, invasive	16
Prior therapy	
Chemotherapy	16
Hormonal therapy	3
Radiation therapy	6
Surgical therapy	7
Prior chemotherapy: number of regimens	
1	4
2	2
3	8
4	2
Number of agents	
≤ 3	3
>3	13

TOXICITY

Liposomal-Annamycin is well tolerated, the dose limiting toxicity being myelosuppression particularly granulocytopenia. The nadir occurs on days 11-14 and in no cases the second dose was delayed. No significant thrombocytopenia was seen. Mild gastrointestinal toxicity such as nausea and vomiting was observed in about 30% of patients and mild mucositis was rare. No alopecia was observed. Fatigue was observed in only a few patients. No events of potential cardiotoxicity were recorded. These results lead to the conclusion that Liposomal-Annamycin is less toxic than the other anthracyclines doxorubicin (Adriamyin) and Daunorubicin.

ANTITUMOR ACTIVITY

No partial responses have been observed in this group of 16 patients. However, only four of these patients received Liposomal-Annamycin as a second line therapy. It is well known that pan-resistance to most agents occurs after 2 and 3 different regiments are given to patients with metastatic solid tumors. As a result, we tried to accrue patients with one prior regimen as adjuvant therapy or for metastatic disease. Unfortunately, this has resulted in a lower accrual because these patients have a number of alternative options. However, we do not believe patients with >2 prior regiment should be entered in the future since we have already demonstrated that there were no responses in 16 such patients.

CORRELATIVE TISSUE STUDIES

Five tissue specimens were obtained pre-therapy for MDR analysis. These samples are kept frozen in Dr. Sahin's laboratory. However, since no responses were observed, the proposed correlation studies can not be performed.

CONCLUSIONS

Results obtained suggest that Liposomal-Annamycin is very well tolerated with grade 3 granulocytopenia being observed in a minority of patients. Non-hematological toxicity is minimal.

No tumor responses have been observed. However, the grand majority of patients had received two or more prior chemo regimens.

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